Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 221 to 282 are pending in the application, with claims 221, 231, 239, 247, 255, and 264 being the independent claims. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejection under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 118 and 119 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Claims 118 and 119 have been canceled, thereby rendering this rejection moot. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Priority Determination

The Examiner alleges that Applicants may claim priority under 35 U.S.C. § 119(e) only back to U.S. Provisional Application No. 60/054,885, filed on August 7 ("the second priority document"), 1997, but not to U.S. Provisional Application No. 60/035,496, filed January 14, 1997 ("the first priority document"). The Examiner contends that the first priority document does not meet the requirements of 35 U.S.C. §§101 and 112, because the specification allegedly does not establish utility for SEQ ID NO:2 according to the current Utility Examination Guidelines, Fed. Reg. 66(4) at 1092-1099 (2001). While the Examiner acknowledges that the first priority document

discloses the protein of SEQ ID NO:2[1], the Examiner still contends that priority cannot be acknowledged because, "there is no ligand or activity for the protein disclosed." Paper No. 22, at 4. Applicants respectfully traverse.

A. Utility Determination under the USPTO *Guidelines*

As an initial comment, Applicants note that the manner of making and using an invention disclosed in a specification, or, as here, a priority document, must be accepted by the PTO "unless there is reason to doubt the objective truth of the statements contained therein." *In re Marzocchi*, 439 F.2d 220, 223, (CCPA 1971); *see also* Utility Examination Guidelines, 66 Fed. Reg. 1092, 1098-99 (January 5, 2001) ("Guidelines"). Furthermore, Applicants respectfully submit that definitive proof of an invention's utility is not required under 35 U.S.C. § 101. "In most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101." M.P.E.P. § 2107.02(III.)(A.) at 2100-39 (Eighth edition, August 2001); *see also In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995) ("[T]he PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure.").

Further, the Federal Circuit has also recently articulated the standard for utility in light of *Brenner*:

> The threshold of utility is not high: An invention is "useful" under section 101 if it is capable of providing

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1 Applicants note that the present application published as US 2001-0021516 A1 (the '516 published application) claiming priority to the January 14, 1997 filing date of the first priority document. Thus, the '516 published application is prior art under 35 U.S.C. § 102(e)(1) against ***all patent applications*** filed by another, after January 14, 1997. **This is true even if the examiner maintains her allegation that the first priority document does not meet the utility requirement.** *See*, for example, *Ex parte Kitamura* 9 USPQ2d 1787 at 1788 (n.2) (BPAI 1988) and *In re Schoenwald* 964 F.2d 1122 at 1124 (Fed. Cir. 1992) which stand for the proposition that a prior art reference need not disclose a utility to anticipate a later filed claim to a compound.

> some identifiable benefit. See *Brenner v. Manson,* 383 U.S. 519, 534 (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.,* 977 F.2d 1555, 1571 (Fed. Cir. 1992) ("To violate § 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger,* 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is capable of serving any beneficial end").

Juicy Whip, Inc. v. Orange Bang Inc., 185 F.3d 1364, 1366, 51 U.S.P.Q.2d 1700, 1702 (Fed. Cir. 1999).

In addition, a *prima facie* showing of no specific and substantial utility "must establish that it is *more likely than not* that a person skilled in the art would not consider that any utility asserted by the applicant would be specific and substantial." Guidelines, 66 Fed. Reg. at 1098 (emphasis added). Applicants respectfully submit that the Examiner has not made the required showing that even one, much less all, of the utilities disclosed for TNFR-5 in the first priority document would be unbelievable in light of the teachings of the document and the knowledge of one skilled in the art -- under either the standard set forth in *Juicy Whip* or the PTO's Guidelines.

Applicants recognize that a claimed invention must possess either a well-established utility or an asserted utility that is specific, substantial and credible. *See* Guidelines, 66 Fed. Reg. at 1098. If the claimed invention has an asserted utility that is specific, substantial and credible utility, or a well-established utility exists for the invention and a utility rejection is improper. *See* "Revised Interim Utility Guidelines Training Materials" (Utility Guidelines), page 9. If, however, Applicants have asserted a utility for the claimed invention in the specification, "[t]he examiner should determine whether any asserted utility is specific and substantial, and if so, whether such utility is credible." Utility Guidelines, page 3.

B. The Present Claims are Entitled to Priority to January 14, 1997

The claims presented herein feature the soluble extracellular portion of TNFR-5. The first priority document discloses several statements that specifically set forth Applicants' assertion of the biological role for the soluble extracellular domain of TNFR-5, and explain why Applicants believe the invention is useful. First, while the first priority document does disclose that members of the TNF-related receptor family typically include an intracellular signaling domain, the disclosure in the first priority document shows that Applicants *clearly* understood that the receptor represented by SEQ ID NO:2 *does not* possess an intracellular signaling domain.[2] For example, the first priority document notes that the polypeptide possessed "a soluble extracellular domain of about 214 amino acids (residues 27-240 of SEQ ID NO:2); and . . . a transmembrane domain of about 19 amino acids (residues 241-259 of SEQ ID NO:2)." The first priority document at page 13, lines 1-3. Furthermore, nowhere in the first priority document is there a suggestion that SEQ ID NO:2 might be a partial sequence which otherwise contains a signaling domain, nor does the first priority document suggest that SEQ ID NO:2 comprises a signaling domain. Finally, by examining SEQ ID NO:1 as shown in the sequence listing submitted with the first priority document, one of ordinary skill in the art would readily appreciate that the cDNA sequence identified in SEQ ID NO:1 is full-length and encodes a complete polypeptide which does not include an intracellular

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2 Prior to January, 1997, a substantial number of human TNF-related receptor ("TNFR") family members had been characterized (Lotz *et al.*, *J. Leukocyte Biol. 60*:1-7 (1996), p. 1, cols. 1 and 2, and first priority document at page 1, line 31 to page 2, line 2) (attached hereto as Exhibit A)). Of particular note, as of January 1997, the majority human TNFRs characterized had sequences which, by their predicted secondary structure, were membrane associated, and had intracellular signaling domains. At this point in time, the reported characterized soluble forms of human TNFRs were either proteolysis derived forms from membrane-bound forms, or splice variants of the membrane bound forms. Lotz *et al.* at p. 1, col. 2. Indeed, the first human TNFR to exclusively exist as a secreted form was not reported in a scientific publication until April, 1997. *See* Simonet *et al.*, *Cell 89*:309-319 (April 1997) (attached hereto as Exhibit C).

signaling domain, because the termination codon at nucleotides 960-962 is only 235 nucleotides upstream of the poly-A tail of the mRNA. In sum, it was clearly appreciated by Applicants and would have been clear to one of ordinary skill in the art upon reading the first priority document, that the TNFR-5 sequence disclosed lacks a signaling domain.

Moreover, references to soluble extracellular forms of TNFR-5 may be found throughout the first priority document, underscoring that Applicants recognized the importance of this form. References include, but are not limited to page 5, lines 12-16; page 6, lines 14-18; Page 13, lines 1-2; page 13, lines 15-27; page 21, lines 1-4 and 15-17; page 29-30 (N terminal deletions); page 31, lines 20-25; page 32, lines 11-20, (C terminal deletions); page 32 line 26 to page 33, line 8; page 34, lines 21-28; and page 38, lines 9-13. In addition, examples 1(a); 2; 3(a); and 3(b) describe the expression of soluble forms of SEQ ID NO:2, (*i.e.*, amino acids 1 to 214) via expression constructs. The 3' primer for amplifying a DNA segment of SEQ ID NO:1 for expression in *E. coli* in example 1(a) binds to nucleotides 902 to 885 of SEQ ID NO:1, which encodes amino acids 209 to 214 of SEQ ID NO:2 (p. 63, line 4), amino acid 214 being the last amino acid in the extracellular domain. The same sequence is contained in the 3' primer for amplifying a DNA segment of SEQ ID NO:1 for expression in the baculovirus system (example 2, page 70, line 25), for expression as an HA fusion protein in COS cells (example 3(a), page 75, line 21), and for expression in CHO cells (example 3(b), page 78, line 22). Finally, claims 1(c), 5, 6, 7, and 19(c) of the first priority document recite nucleotide sequences encoding polypeptides, or polypeptides comprising the soluble extracellular domain of SEQ ID NO:2.

More importantly, at the time of the first priority document Applicants had clearly established a specific and substantial utility for the soluble extracellular form of TNFR-5, as an antagonist of TNFR activity, *i.e.*, to "antagonize TNFR mediated signaling by competing with the cell surface TNFR for binding to TNF-family ligands" to, for example, "inhibit tumor necrosis induced by TNF-family ligands." First priority document at p. 54, lines 31-33; *see also* first priority document at page 51, lines 24-33, and at page 54, lines 28-35.[3] Given the established skill in the art, Applicants respectfully point out that this asserted utility would not have required knowledge of the specific ligand which binds TNFR-5. As of January, 1997, standard cell-based assays were available to assess the cellular responses such as apoptosis evoked by various TNF-family ligands and receptors. *See, e.g.*, Lotz *et al.* at pages 3-5, and Wiley *et al.*, at page 675-676. These assays could be easily and routinely performed by one of ordinary skill in the art. Furthermore, the first priority document discloses assays to screen for antagonist activity against various TNFR biological functions, which could be easily modified to use in various TNF-like receptor-ligand systems such as those disclosed in Lotz *et al.* and Wiley *et al.* *See, e.g.*, first priority document at p. 51, line 34, through page 53, line 20. Thus, without knowing the ligand which binds TNFR-5, using the methods and assays disclosed in the first priority document, one of ordinary skill in the art could easily and routinely perform screening assays using the approximately 10

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3 Prior to January 1997, approximately 10 members of the TNF-like ligand family had been reported in peer reviewed scientific publications, including TRAIL, a TNF-ligand family member that was known to induce apoptosis in a wide variety of transformed cell lines. First priority document at page 1, lines 28-30; Lotz *et al.* at p. 1, and Wiley *et al.*, *Immunity* 3:673-682 (1995). TRAIL (but not its receptor) was first described in Wiley *et al.*, *Immunity* 3:673-682 (1995) (attached hereto as Exhibit B). With the exception of TRAIL, a TNF-like receptor family member had been identified for TNF-ligand family mambers that were reported in these publications. See, e.g., Lotz et al., Table 1, page 2. Additionally, molecular binding assays and cell-based assays to screen for cellular responses elicited by the ligands, such as apoptosis and tumor necrosis, were known.

known TNF-family ligands to screen for cellular responses such as apoptosis and tumor necrosis which are inhibited by the soluble extracellular domain of TNFR-5. Thus, the first priority document discloses a specific and substantial utility, as well as a well-established utility for the soluble extracellular domain of TNFR-5 as an antagonist of TNFR activity.

For the reasons discussed above regarding utility under 35 U.S.C. § 101, Applicants further assert that the first priority document further meets the requirements of 35 U.S.C. § 112, first paragraph with respect to the presently claimed invention. The Examiner "should not impose a 35 U.S.C. 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. 101 rejection is proper." M.P.E.P. § 2107.01 at 2100-36. Therefore, since the first priority document complies with the utility requirement of 35 U.S.C. § 101 with respect to the pending claims, the rejection under 35 U.S.C. § 112, first paragraph, based on the alleged lack of utility of the claimed invention, should be withdrawn.

For the reasons discussed above, Applicants respectfully assert that pending claims in the present application are clearly entitled to the benefit of the filing date of provisional application No. 60/035,496 under 35 U.S.C. § 119(e). Accordingly, acknowledgement of priority to January 14, 1997 is respectfully requested.

Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 117-220 under 35 U.S.C. § 102(e) as allegedly being anticipated by Ashkenazi *et al.*, U.S. Patent Application Publication No. 2002/0161202 ("the '202 publication"). Based on Applicants' arguments regarding priority, *supra*, Applicants respectfully traverse. Claims 117-220 have been canceled,

claims 221-282 are pending. As discussed above, Applicants are entitled to claim priority to the first priority document, filed January 14, 1997 under 35 U.S.C. § 119(e). Accordingly, the effective filing date for the pending claims presented herein is January 14, 1997. Thus, the '202 publication, the earliest possible effective filing date of which is June 18, 1997, cannot anticipate the pending claims.

Based on these remarks, Applicants respectfully request that the 102(e) rejection be reconsidered, and further, that it be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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